
Efficacy and Safety of Elobixibat on Constipation in End-Stage Kidney Disease Patients Undergoing Hemodialysis: A Randomized Controlled Trial

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Abstract

Background: Chronic constipation is prevalent among patients with end-stage kidney disease (ESKD). Recently, elobixibat, a novel inhibitor of the ileal bile acid transporter, has been used to treat chronic constipation by stimulating bowel function. However, its efficacy and safety in ESKD patients undergoing hemodialysis (HD) have yet to be examined.

Methods: HD patients diagnosed with chronic constipation, as per the Rome IV criteria, were randomized in a 1:1 allocation ratio to receive either elobixibat or a placebo for 12 weeks. Changes in the Bristol Stool Form Scale (BSFS), frequencies of spontaneous bowel movements (SBM) and complete spontaneous bowel movements (CSBM) per week, LDL cholesterol levels, and the gut microbiota-derived metabolite, P-cresol, from baseline were evaluated after the 12-week period.

Results: A total of 46 patients participated in the study. After 12 weeks of treatment, significant improvements were observed in the BSFS (mean difference [95% confidence interval] = 1.93 [1.37, 2.48], $P < 0.001$), and there was an increase in the frequencies of SBM (2.46 [1.69, 3.23], $P < 0.001$) and CSBM (2.83 [1.63, 3.39], $P < 0.001$) per week in the elobixibat group compared with the placebo group. Additionally, LDL cholesterol levels significantly decreased in the elobixibat group relative to the placebo group (-12.41 [-24.72, -0.09], $P < 0.001$). No significant differences were noted in other laboratory data or P-cresol levels. Furthermore, no serious adverse events were reported in either group.

Conclusion: Elobixibat exhibited an efficacy in improving constipation and reducing LDL cholesterol levels. These findings suggest that elobixibat might be an effective treatment for chronic constipation in ESKD patients undergoing HD.

Keywords: bowel movement; dialysis; chronic kidney disease; CKD; ESRD

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การศึกษาประสิทธิภาพและความปลอดภัยของอีโลบิซิเบตต่อภาวะท้องผูกในผู้ป่วยโรคไตเรื้อรังระยะสุดท้ายที่ได้รับการรักษาด้วยการฟอกเลือดด้วยเครื่องไตเทียม: การศึกษาแบบสุ่มและมีกลุ่มควบคุม

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บทคัดย่อ

บทนำ: ภาวะท้องผูกเรื้อรังเป็นภาวะที่พบได้บ่อยในผู้ป่วยโรคไตเรื้อรังระยะสุดท้าย ยาอีโลบิซิเบตเป็นยาระบายชนิดใหม่ที่ออกฤทธิ์ยับยั้งการดูดซึมกรดน้ำดีที่ลำไส้ และถูกนำมาใช้ในการรักษาภาวะท้องผูกเรื้อรังโดยจะไปช่วยกระตุ้นการทำงานของลำไส้ อย่างไรก็ตามยังไม่มีการศึกษาประสิทธิภาพและความปลอดภัยของยาก่อนหน้านี้ในผู้ป่วยโรคไตเรื้อรังระยะสุดท้ายที่ได้รับการฟอกเลือดด้วยเครื่องไตเทียม

ระเบียบวิธีวิจัย: การศึกษาแบบสุ่มและมีกลุ่มควบคุมในผู้ป่วยที่ได้รับการฟอกเลือดด้วยเครื่องไตเทียมที่มีภาวะท้องผูกเรื้อรังโดยวินิจฉัยตามเกณฑ์ Rome IV ผู้ป่วยถูกจัดเข้าสู่กลุ่มอีโลบิซิเบตหรือยาหลอกแบบสุ่มในอัตราส่วน 1:1 เป็นระยะเวลา 12 สัปดาห์ มีการประเมินการเปลี่ยนแปลงของ Bristol stool form scale (BSFS), จำนวนครั้งของการถ่ายอุจจาระ และ จำนวนครั้งของการถ่ายอุจจาระที่รู้สึกถ่ายสุดต่อสัปดาห์, ระดับ LDL cholesterol และ P-cresol ก่อนและหลังจากได้รับการรักษาไปแล้ว 12 สัปดาห์

ผลการศึกษา: มีผู้ป่วยเข้าร่วมการศึกษาทั้งหมด 46 ราย หลังจากได้ยาที่ 12 สัปดาห์พบว่ากลุ่มอีโลบิซิเบตมี BSFS ดีขึ้นมากกว่ากลุ่มยาหลอกอย่างมีนัยสำคัญทางสถิติ (mean difference (95% confidence interval) = 1.93 (1.37, 2.48), $P < 0.001$) มีการเพิ่มขึ้นของจำนวนครั้งของการถ่ายอุจจาระ (2.46 (1.69, 3.23), $P < 0.001$) และจำนวนครั้งของการถ่ายอุจจาระที่รู้สึกถ่ายสุดต่อสัปดาห์ (2.83 (1.63, 3.39), $P < 0.001$) ในกลุ่มที่ได้รับอีโลบิซิเบตอย่างมีนัยสำคัญทางสถิติ นอกจากนี้ยังพบว่าการลดลงของระดับ LDL cholesterol เปรียบเทียบกับยาหลอก (-12.41 (-24.72, -0.09), $P < 0.001$) แต่ไม่พบความแตกต่างของการเปลี่ยนแปลงของระดับ P-cresol และไม่พบผลข้างเคียงของยาที่รุนแรง

สรุป: ยาอีโลบิซิเบตช่วยลดอาการท้องผูกและระดับ LDL cholesterol ในผู้ป่วยที่ได้รับการฟอกเลือดด้วยเครื่องไตเทียม ผลการศึกษานี้แสดงให้เห็นถึงประสิทธิภาพของยาอีโลบิซิเบตในการรักษาภาวะท้องผูกเรื้อรัง

คำสำคัญ: การบำบัดทดแทนไต; โรคไตเรื้อรัง; ไตวาย; อุจจาระ

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Introduction

Chronic constipation is common among patients with end-stage kidney disease (ESKD) undergoing hemodialysis (HD).¹ The prevalence of constipation in dialysis patients exceeds that in the general population and is associated with adverse clinical outcomes, including decreased quality of life, increased cardiovascular events, and elevated mortality rates.²⁻⁵ The causes of constipation in dialysis patients are multifactorial. Factors such as fluid restriction, excessive fluid removal during dialysis, inadequate dietary fiber intake, the use of phosphate and potassium binders, and comorbidities like diabetes collectively contribute to chronic constipation in these patients. Additionally, alterations in intestinal microbiota and the accumulation of gut-derived uremic toxins further exacerbate constipation.⁶⁻¹⁰

The use of laxatives presents challenges in ESKD patients. Magnesium oxide is contraindicated due to the risk of hypermagnesemia.¹¹ Bulk-forming laxatives are not advisable due to associated fluid intake concerns. Furthermore, the efficacy of anthraquinone stimulant laxatives diminishes with prolonged use.¹² Hence, the pharmacological management of constipation in dialysis patients requires careful consideration.¹³

Elobixibat stands out as a novel, locally acting laxative. Acting as an inhibitor of the bile acid transporter (IBAT) expressed specifically in the terminal ileum, elobixibat disrupts the enterohepatic circulation of bile acids. This disruption stimulates bile acid synthesis in the liver, leading to increased bile acid concentrations in the colon lumen, thereby enhancing colonic motility and fluid secretion.¹⁴ Recent observational studies have indicated that elobixibat ameliorates constipation symptoms, including enhancing the frequency of spontaneous bowel movements (SBM) and improving scores on the Bristol Stool Form Scale (BSFS) among dialysis patients with functional constipation.¹⁵⁻¹⁷ Additionally, some studies have reported reductions in LDL-cholesterol and serum phosphate levels following elobixibat administration.¹⁷⁻¹⁹ However, to date, no randomized controlled trial has assessed the efficacy of elobixibat in dialysis patients with chronic constipation,

nor has its impact on LDL-cholesterol and the gut-derived uremic toxin, P-cresol, been thoroughly evaluated. Consequently, the current study seeks to investigate the efficacy of elobixibat in HD patients suffering from chronic constipation.

Materials and Methods

The present study was a randomized, single-center, double-blind, placebo-controlled trial involving ESKD patients undergoing maintenance HD from July 1, 2022, to February 1, 2023. Following an initial 1-week run-in period, eligible patients were randomized in a 1:1 allocation ratio to receive either elobixibat or a placebo for 12 weeks.

Outcomes

The primary outcome measure was the mean change in the BSFS at 2 weeks. Secondary outcomes included changes in the BSFS, frequencies of spontaneous bowel movements (SBM), complete spontaneous bowel movements (CSBM) (defined as spontaneous bowel movements with a sense of complete evacuation) per week, and other laboratory data, including P-cresol levels, after 12 weeks.

Participants

Participants were receiving maintenance HD at Phramongkutklao and Thian Fah Foundation hospitals. The research proposal underwent review by the Sub-Committee to Consider the Research Proposal of the Royal Thai Army Medical Department. All participants provided signed informed consent. Eligibility criteria included: (1) age >20 years; (2) receiving maintenance HD for >3 months; (3) adequate dialysis (spKT/V > 1.2); and (4) functional constipation as defined by the Rome IV criteria. Exclusion criteria encompassed chronic constipation resulting from: (1) organic disorders, including neurologic, endocrine, or metabolic diseases; (2) mechanical obstruction or intestinal surgery, excluding simple appendectomy; (3) irritable bowel syndrome; or (4) other medical conditions such as cancers, biliary obstruction, cirrhosis, or pregnancy.

Randomization

Eligible patients were randomized in a 1:1 allocation ratio using a computerized block of four randomization

sequences to receive either elobixibat or a placebo. Elobixibat at a dosage of 10 mg per day (2 tablets) or a placebo was administered before bedtime over a 12-week period. Elobixibat and placebo tablets were provided in sealed, opaque packages, each labeled with a randomization number and prescription. This method ensured double blinding, thereby maintaining the blinding of investigators and patients at both participating hospitals.

Outcome assessments

Stool consistency was assessed using the seven-point BSFS scale. Frequencies of SBM and CSBM per week were evaluated at baseline, 2 weeks post-randomization, and after 12 weeks. Changes in laboratory data, including LDL cholesterol and P-cresol levels, were assessed both at baseline and after 12 weeks.

Sample size calculation

The sample size was determined based on the mean change in stool consistency score observed in a previous trial. A sample size of 19 patients per group was calculated to achieve 90% power for testing the hypothesis that a difference existed in the primary outcome between groups, with a two-sided α of 0.05. To

account for potential withdrawals, an additional 20% of patients were enrolled in each group.

Statistical analysis

Data were analyzed using an intention-to-treat approach. Mean and standard deviation were utilized for continuous data with a normal distribution, while median and interquartile range were employed for data not following a normal distribution. Inferential statistics were applied to compare baseline demographic and laboratory data. Categorical variables were compared using the Chi-square test or Fisher's exact test, whereas continuous variables were assessed using either the Student's t-test or the Mann-Whitney U test, as appropriate. Between-group changes were evaluated using repeated measures ANOVA. A p-value of <0.05 was deemed statistically significant.

Results

The study flow chart is shown in **Figure 1**. A total of 46 patients were included. Three patients withdrew consent during the study: one from the elobixibat group and two from the placebo group.

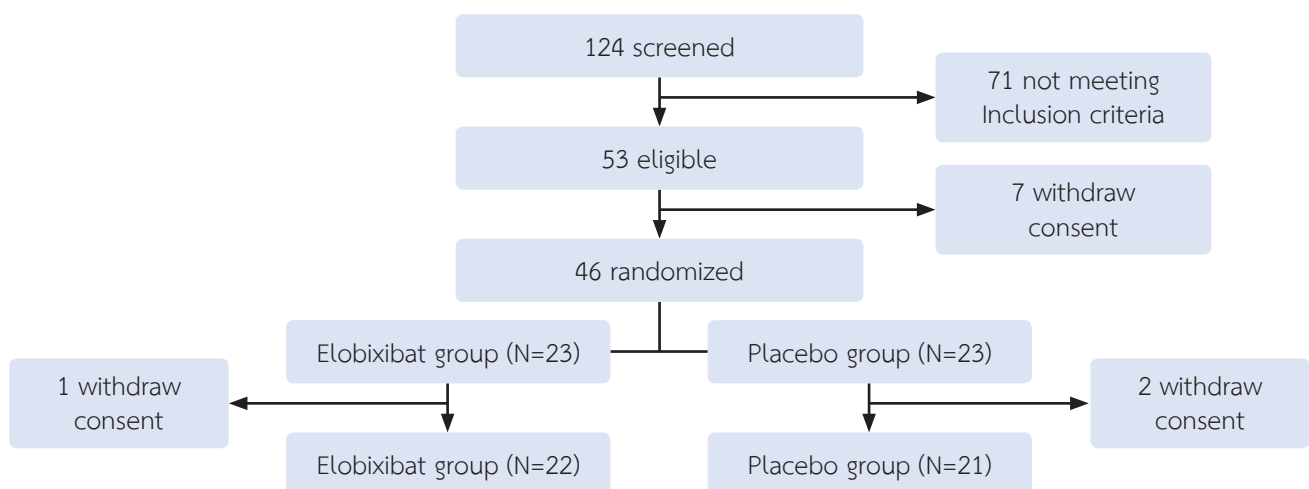


Figure 1 Study Flow Chart

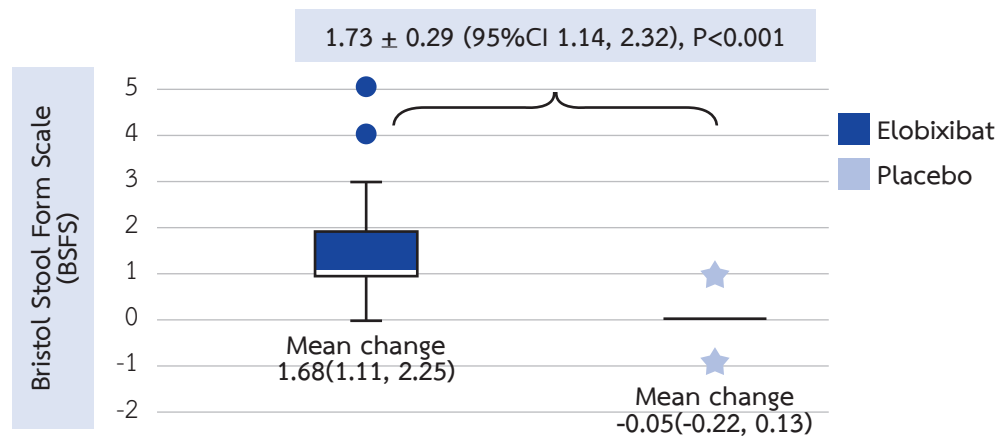
Baseline characteristics of all patients are shown in **Table 1**. Fifty-eight percent of the patients were male. The mean age was 58 years. The most common causes of ESKD were diabetes mellitus and hypertensive nephrosclerosis. Symptoms of constipation, including

the BSFS, frequencies of SBM, and CSBM per week during the run-in period, did not differ between the two groups. Additionally, other laboratory data, such as LDL cholesterol and P-cresol levels, were also similar.

Table 1 Baseline characteristics and laboratory data of all patients

Variable	Elobixibat	Placebo	P-value
Male (N,%)	14 (63.6%)	11 (52.4%)	0.45
Age (years)	57.73 ± 11.83	59.14 ± 12.99	0.71
Body mass index (kg/m ²)	22.53 ± 4.9	22.67 ± 4.39	0.92
Causes of kidney failure (N,%)			
Diabetic nephropathy	7 (31.8%)	9 (42.9%)	0.51
Hypertensive nephrosclerosis	10 (45.5%)	9 (42.9%)	
Glomerulonephritis	2 (9.1%)	0 (0%)	
Hemodialysis vintage (years), median (IQR)	3 (1-5)	4 (2-9)	0.30
spKT/V, median (IQR)	1.5 (1.4-1.6)	1.4 (1.3-1.5)	0.10
Systolic blood pressure (mmHg)	146 ± 22.22	153.57 ± 16.55	0.21
Diastolic blood pressure (mmHg)	73.27 ± 14.11	70.43 ± 10.18	0.45
Bristol stool form scale	2.68 ± 1.17	2.14 ± 1.2	0.14
Spontaneous bowel movement/week	3.82 ± 1.53	3.95 ± 1.91	0.80
Complete spontaneous bowel movement/week	1.23 ± 1.27	1.14 ± 1.49	0.84
Laxative drugs (N,%)			
Sennosides	10 (45.5%)	11 (52.4%)	0.35
Lactulose	1 (4.5%)	4 (19%)	
Bisacodyl	1 (4.5%)	0 (0%)	
Fiber (N/%)	0 (0%)	1 (4.8%)	
Sennosides+ lactulose (N/%)	2 (9.1%)	1 (4.8%)	
Iron supplement (N/%)	12 (54.5%)	8 (38.1%)	0.28
Phosphate binders (N/%)			
Calcium carbonate	15 (68.2%)	15 (71.4%)	0.41
Sevelamer	1 (4.5%)	0 (0%)	
Aluminum	0 (0%)	2 (9.5%)	
Calcium+ Sevelamer	1 (4.5%)	1 (4.8%)	
Calcium+ Aluminum	2 (9.1%)	0 (0%)	
Hemoglobin (g/dL)	9.84 ± 1.62	10.24 ± 1.6	0.43
Blood urea nitrogen (mg/dL)	60.31 ± 15.11	62.03 ± 15.68	0.72
Creatinine (mg/dL)	9.2 ± 3.02	9.33 ± 2.28	0.87
Sodium (mEq/L)	134.77 ± 2.52	135 ± 3.53	0.81
Potassium (mEq/L)	4.75 ± 0.84	4.71 ± 0.63	0.85
Chloride (mEq/L)	96.5 ± 2.81	94.95 ± 3.64	0.13
Bicarbonate (mEq/L)	23.59 ± 2.06	23.05 ± 2.46	0.45
Calcium (mg/dL)	9.21 ± 0.89	9.27 ± 1.14	0.85
Phosphate (mg/dL)	4.79 ± 1.5	5.01 ± 1.78	0.67
Magnesium (mg/dL)	2.22 ± 0.3	2.31 ± 0.33	0.37
Albumin (g/dL)	4.01 ± 0.36	4.31 ± 0.38	0.01*
Low density lipoprotein (mg/dL)	103.77 ± 54.33	89.98 ± 27.51	0.32
P-cresol (mg/L)	7.37 ± 5.56	5.89 ± 4.01	0.32

The elobixibat group exhibited a statistically significant increase in the BSFS at 2 weeks [mean difference (95% CI) = 1.68 (1.11 to 2.25), p-value < 0.001]. In contrast, the placebo group showed no significant change [-0.05 (-0.22 to 0.13), p-value = 0.57]. A between-group comparison revealed a significant difference in the changes in BSFS from baseline [elobixibat vs. placebo = 1.73 ± 0.29 (1.14, 2.32), p-value < 0.001] (Figure 2).



All data are expressed as Mean with 95%CI

Figure 2 Mean difference in BSF Scale at 2 weeks

Table 2 presents the secondary outcomes at 12 weeks. The between-group changes in the BSFS (elobixibat vs. placebo) were 1.93 ± 0.27 (95% CI = 1.37, 2.48; p-value < 0.001), the frequency of SBM per week was 2.46 ± 0.38 (95% CI = 1.69, 3.23; p-value < 0.001), and the frequency of CSBM per week was 2.83 ± 0.43 (95% CI = 1.96, 3.71;

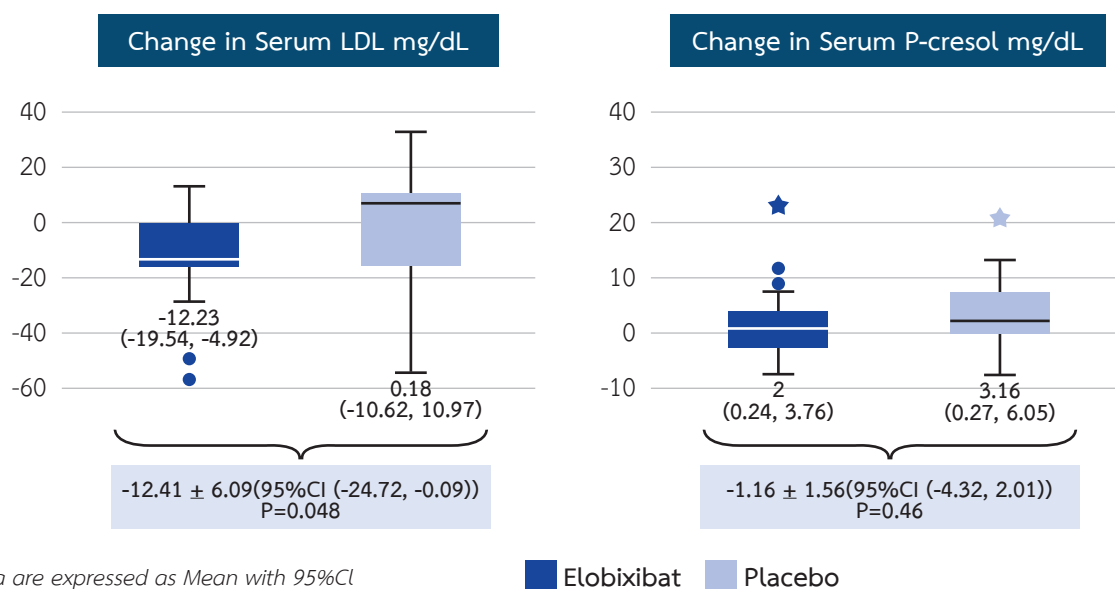
p-value < 0.001). Additionally, the elobixibat group exhibited a significant reduction in LDL cholesterol compared to the placebo group (-12.41 ± 6.09 ; 95% CI = -24.72, -0.09; p = 0.048). No significant changes were observed in P-cresol levels or other laboratory data (**Table 3 and Figure 3**).

Table 2 The changes in constipation symptoms at 12 weeks

Variable	Elobixibat	Placebo	P-value
Bristol Stool Form Scale			
Baseline	2.68 ± 1.17	2.14 ± 1.2	< 0.001
12 weeks	4.41 ± 1.05	2 ± 0.92	
Mean change from baseline	$1.73 (1.27, 2.18)$	$-0.2 (-0.53, 0.13)$	
Significance within the same group	< 0.001	0.214	
Spontaneous Bowel Movement per week			
Baseline	3.82 ± 1.53	3.95 ± 1.91	< 0.001
12 weeks	5.23 ± 1.31	2.95 ± 1.76	
Mean change from baseline	$1.41 (0.79, 2.03)$	$-1.05 (-1.54, -0.56)$	
Significance within the same group	< 0.001	< 0.001	
Complete spontaneous bowel movement per week			
Baseline	1.23 ± 1.27	1.14 ± 1.49	< 0.001
12 weeks	3.91 ± 1.48	1.05 ± 0.94	
Mean change from baseline	$2.68 (1.93, 3.44)$	$-0.15 (-0.64, 0.34)$	
Significance within the same group	< 0.001	0.527	

Table 3 Mean differences of laboratory data at 12 weeks

Laboratory data	Elobixibat	Placebo	P-value
Hemoglobin (g/dL)	0.04 (-0.45, 0.52)	0 (-0.86, 0.86)	0.937
Blood urea nitrogen (mg/dL)	-3.16 (-9.66, 3.33)	-3.61 (-11.6, 4.38)	0.927
Creatinine (mg/dL)	-0.45 (-1.07, 0.16)	-0.54 (-1.31, 0.22)	0.844
Sodium (mEq/L)	0.5 (-1.3, 2.3)	1.36 (0.09, 2.63)	0.436
Potassium (mEq/L)	-0.09 (-0.49, 0.32)	0.24 (-0.01, 0.5)	0.175
Bicarbonate (mEq/L)	-0.55 (-1.73, 0.64)	-0.21 (-1.5, 1.08)	0.691
Phosphate (mg/dL)	-0.35 (-0.92, 0.22)	0.26 (-0.21, 0.74)	0.101

**Figure 3** Mean differences in LDL cholesterol and P-cresol at 12 Weeks

One patient in the placebo group reported abdominal pain. None of the patients reported nausea, vomiting, diarrhea, hepatitis, or any other side effects.

Discussion

The present study demonstrated significant improvement in constipation symptoms, including BSFS, frequencies of SBM, and CSBM, in the elobixibat group compared to the placebo group. Moreover, a notable reduction in LDL concentration was observed in the elobixibat group.

The short-term treatment effects of elobixibat align with previous observational studies that reported

increased SBM frequency and improved stool consistency in HD patients with chronic constipation.¹⁵⁻¹⁷ A recent Phase 3 randomized controlled trial in patients with normal renal function also indicated that elobixibat enhanced the frequency of SBM and stool consistency score.¹⁸

The reduction in LDL cholesterol concentration in our study can be attributed to increased bile acid excretion into the intestinal lumen due to IBAT inhibition. This heightened bile acid excretion stimulates bile acid production from cholesterol in the liver, leading to reduced LDL cholesterol levels. Our findings align with prior studies.¹⁷ Notably, some studies have indicated that elobixibat could increase HDL cholesterol

in HD patients. In a randomized controlled trial involving patients with normal renal function, elobixibat reduced LDL cholesterol without significantly affecting HDL cholesterol.¹⁸ This suggests that elobixibat's impact on LDL is not exclusive to ESKD patients.

Some studies have reported about a 10% reduction in serum phosphate following elobixibat use.¹⁹ However, our study did not observe any changes in serum phosphate levels. Further research is essential to determine elobixibat's effect on phosphate metabolism.

Several limitations characterize our study. Firstly, it was a single-center study, potentially limiting external validation. Secondly, the study's duration was brief, precluding a long-term safety assessment. Thirdly, with a fixed elobixibat dose of 10 mg/day, we lacked data on the dose-response relationship concerning constipation symptoms. Fourthly, while elobixibat might reduce other gut-derived uremic toxins, our study solely focused on P-cresol levels. Lastly, the use of other laxatives in the placebo group may have confounded results, given that 60% of placebo group patients required rescue therapy during the study.

Conclusion

Elobixibat effectively improved constipation symptoms and reduced LDL cholesterol in ESKD patients undergoing HD. In this short-term study, elobixibat emerged as a safe and efficacious treatment for chronic constipation.

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